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RESEARCH ARTICLE

Personalized Antibodies for Gastroesophageal Adenocarcinoma (PANGEA): A Phase II Study Evaluating an Individualized Treatment Strategy for Metastatic Disease

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ABSTRACT

The one-year and median overall survival (mOS) rates of advanced gastroesophageal adenocarcinomas (GEA) are ~50% and <12 months, respectively. Baseline spatial and temporal molecular heterogeneity of targetable alterations may be a cause of failure of targeted/immunooncologic therapies. This heterogeneity, coupled with infrequent incidence of some biomarkers, has resulted in stalled therapeutic progress. We hypothesized that a personalized treatment strategy, applied at first diagnosis then serially over up to three treatment lines using monoclonal antibodies combined with optimally sequenced chemotherapy, could contend with these hurdles. This was tested using a novel clinical expansion-platform type II design with a survival primary endpoint. Of 68 patients by intention-to-treat, the one-year survival rate was 66% and mOS was 15.7 months, meeting the primary efficacy endpoint (one-sided $P = 0.0024$). First-line response rate (74%), disease control rate (99%), and median progression-free survival (8.2 months) were superior to historical controls. The PANGEA strategy led to improved outcomes warranting a larger randomized study.

SIGNIFICANCE: This study highlights excellent outcomes achieved by individually optimizing chemotherapy, biomarker profiling, and matching of targeted therapies at baseline and over time for GEA. Testing a predefined treatment strategy resulted in improved outcomes versus historical controls. Therapeutic resistance observed in correlative analyses suggests that dual targeted inhibition may be beneficial.

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INTRODUCTION

Gastroesophageal adenocarcinoma (GEA) is a significant global health problem (1). Despite palliative chemotherapy, median overall survival (mOS) of advanced disease is less than one year (2). The anti-HER2 antibody trastuzumab demonstrated improved mOS of 14 to 16 months for first-line *HER2*-amplified and -overexpressed GEA, yet the one-year survival rate was still less than 65% (3). Next-generation sequencing (NGS) identified interpatient molecular heterogeneity with a number of often rare and/or frequently co-occurring biological subgroups within GEA, including tumors harboring amplifications of key receptor tyrosine kinases (RTK) other than *HER2*, including *EGFR, MET*, and *FGFR2*, and also downstream MAPK/PIK3CA pathway activations (4). Higher PD-L1 expression levels and high microsatellite instability (MSI-high) were associated with enriched therapeutic benefit from anti–PD-1 therapies in small series (5). However, numerous targeted therapies and immunotherapies failed in the first and later treatment lines for GEA, including but not limited to anti-HER2 therapy beyond first progression, anti-EGFR, anti-MET, antiangiogenesis, and anti–PD-1/PD-L1 therapies (6–15). A potential contributing explanation for these failed attempts included molecular heterogeneity (16), not only between patients (4) but also spatially within patients at baseline (17), and over time after generation of therapeutic resistance (18).

Novel clinical trial designs attempting to address molecular heterogeneity have been described (16, 19) and are often referred to as basket, umbrella, or expansion-platform studies, the latter because they expand on previous preclinical and clinical evidence supportive of specific biomarker–treatment pairings. Most of these studies to date have been type I expansion studies, those focused on molecular heterogeneity between patients, whereby after identifying patients with a given genomic alteration, classic study designs and statistical methods are then applied to each substudy (16). The general advantage of such type I studies, whether histology-dependent (type Ia) or agnostic (type Ib), is the coordinated molecular profiling and screening such that many parallel studies can then be simultaneously conducted downstream for various molecular subgroups. Histology-agnostic studies have the added benefit of pooling across tumor types to enhance accrual of low-incidence genomic alterations. Disadvantages, however, include persistent difficulty in enrolling adequate numbers of patients to low-incidence groups (20), heterogeneous treatment standards making earlier-line combination studies challenging, and also the added prognostic and predictive heterogeneity by including differing tumor histologies. Furthermore, type I expansion studies have generally been conducted in later treatment lines as monotherapy, making them less likely to be effective. Importantly, type I expansion studies have largely not addressed baseline spatial and temporal intrapatient molecular heterogeneity. Thus, no clinical trials

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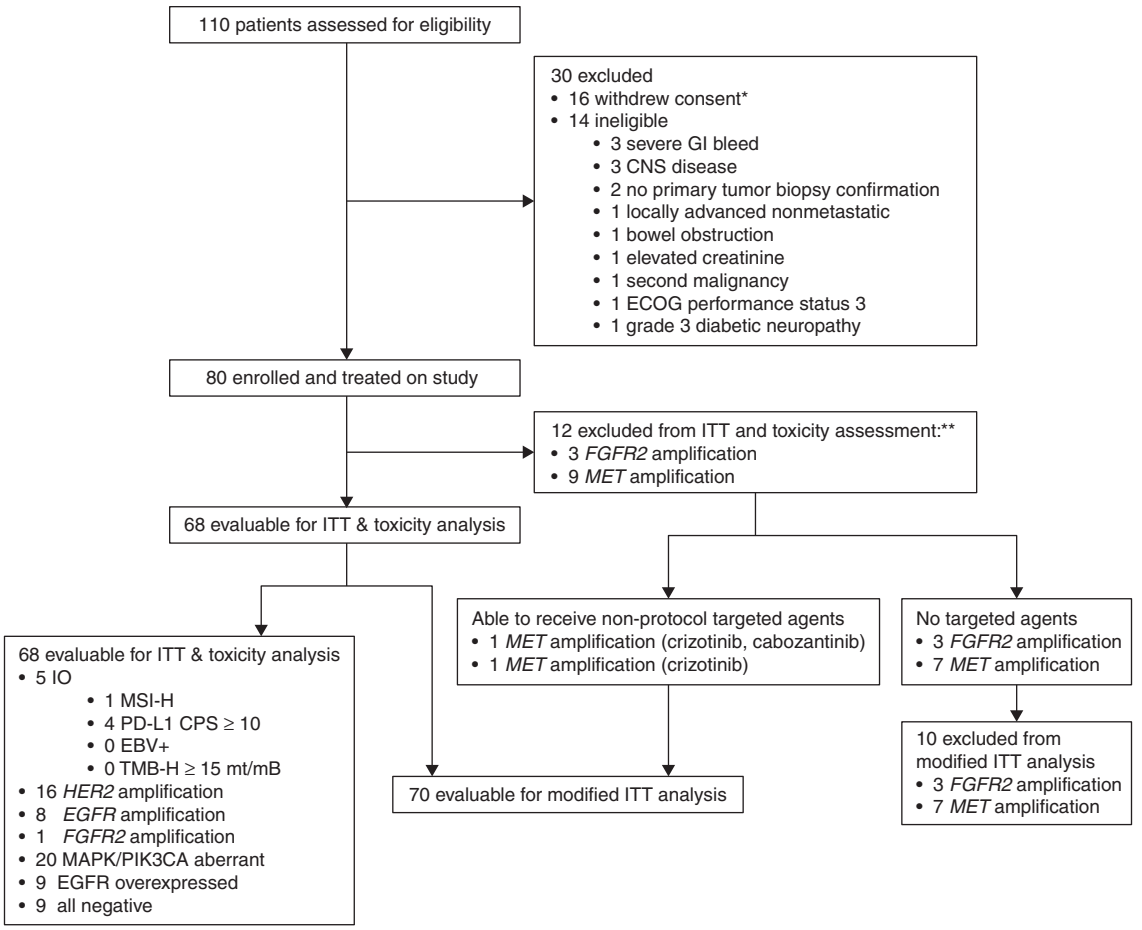

Figure 1. CONSORT diagram. ITT, intention to treat; mITT, modified ITT; GI, gastrointestinal; CNS, central nervous system; ECOG, Eastern Cooperative Group; IO, immuno-oncology; MSI-H, microsatellite instability high; CPS, combined positivity score; EBV+, Epstein–Barr virus–positive; TMB, tumor mutation burden; mt/mB, mutations per megabase. *, The most common reason for consent withdrawal was patient decision to enroll in other competing immunotherapy-based first-line studies. **, Patients without availability of monoclonal antibody due to inability to secure collaborative agreement in the *MET* and *FGFR2* groups were treated, per protocol, with standard therapy and followed for outcome. Patients able to get off-label matched targeted therapy (two patients harboring *MET*-amplified tumors) were evaluated in a preplanned mITT analysis.

have systematically and simultaneously tackled molecular heterogeneity in totality—not only between patients but also within patients at first baseline diagnosis as well as after development of treatment resistance. A novel approach, termed a type II expansion-platform study, was described to prospectively test a personalized treatment strategy incorporating individualized treatments for each patient at baseline and over sequential lines of therapy (16, 21, 22).

Generally, therapeutic monoclonal antibodies such as trastuzumab are easily combined and work synergistically with cytotoxic chemotherapy with low risk of off-target effects and consequently less added toxicity compared with other targeted agents such as small-molecule inhibitors (3, 23, 24). In addition to ligand-blocking activity coupled with receptor binding, internalization, and degradation by monoclonal antibodies, another important putative mechanism of action includes antibody-dependent cell-mediated cytotoxicity (ADCC), recruiting innate immune effector cells to the tumor microenvironment (25, 26).

We sought to optimize survival using sequential doublet cytotoxic therapy in combination with an individually matched monoclonal antibody at baseline diagnosis, then again serially over up to three lines of therapy in a phase II expansion-platform type II clinical trial of personalized antibodies for gastroesophageal adenocarcinoma (PANGEA; refs. 16, 22, 27, 28). To preemptively address the possibility of multiple therapeutic options due to concurrent molecular alterations in a given patient's sample, a predefined prioritized biomarker and treatment assignment algorithm was applied at each therapeutic line. We hypothesized that this personalized treatment strategy, entailing eight biological subgroups with six matched monoclonal antibodies, could contend with the formidable hurdles posed by interpatient and intrapatient molecular heterogeneity, leading to improved outcomes compared with historical controls.

RESULTS

Patient Characteristics and Disposition

Over four years between June 2015 and May 2019, 80 eligible patients were enrolled and included in the analysis at the time of the final data lock, August 20, 2020, of whom 68 were included in the intention-to-treat (ITT) analysis (Fig. 1 and Table 1). Poor prognostic features including Eastern

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Table 1. Baseline clinicopathologic characteristics of all patients enrolled and by ITT

Characteristic	All patients enrolled ($n = 80$)	ITT-PTS ($n = 68$)	Non-ITT ($n = 12$)
Median age (range)	61 (28–81)	61 (28–81)	61 (39–77)
Gender			
Male	64 (80%)	53 (78%)	11 (92%)
Female	16 (20%)	15 (22%)	1 (8%)
Primary tumor			
Non-cardia stomach	30 (38%)	18 (26%)	8 (67%)
EGJ (Siewert I/II/III)	50 (63%)	50 (74%)	4 (33%)
Anatomic location			
Esophagus	34 (43%)	32 (47%)	2 (17%)
GEJ	24 (30%)	18 (26%)	6 (50%)
Cardia	4 (5%)	3 (4%)	1 (8%)
Body	7 (8.8%)	7 (10%)	—
Antrum	7 (8.8%)	5 (7%)	2 (17%)
Pylorus	1 (1%)	1 (1%)	—
Linitis Plastica	3 (4%)	2 (3%)	1 (8%)
Signet ring cells			
Present	21 (26%)	20 (29%)	1 (8%)
Absent	59 (74%)	48 (71%)	11 (92%)
Tumor differentiation			
G1 Well	3 (4%)	3 (4%)	—
G2 Moderately	26 (33%)	25 (37%)	1 (8%)
G3 Poorly	51 (64%)	40 (59%)	11 (92%)
Baseline metastasis[a]			
LN	50 (63%)	41 (60%)	9 (75%)
Peritoneum	30 (38%)	26 (38%)	4 (33%)
Liver	29 (36%)	25 (37%)	4 (33%)
Lung	6 (8%)	5 (7%)	1 (8%)
Bone	4 (5%)	3 (4%)	1 (8%)
Adrenal gland	3 (4%)	3 (4%)	—
Other	1 (1%)	1 (1%)	—
Prior primary surgery			
Yes	8 (10%)	8 (11.8%)	—
No	72 (90%)	60 (88.2%)	12 (100%)
Race			
Hispanic:	4 (5%)	4 (6%)	—
Non-Hispanic	76 (95%)	64 (94%)	12 (100%)
Asian	2 (2.5%)	2 (3%)	—
Black	7 (8.8%)	7 (10%)	—
White	68 (85%)	57 (84%)	11 (92%)
More than one race	3 (3.8%)	2 (3%)	1 (8%)
Performance status			
0	40 (50%)	35 (51%)	5 (42%)
1	33 (41%)	28 (41%)	5 (25%)
2	7 (9%)	5 (7%)	2 (17%)

Abbreviations: ITT-PTS, intention to treat by personalized treatment strategy for patients having monoclonal antibodies readily available; non-ITT, those patients in biomarker groups 4 (FGFR2) and 5 (MET) who did not have available monoclonal antibodies and therefore treated with standard therapy only and followed for outcomes; EGJ, esophagogastric junction including Siewert type I–III; GEJ, gastroesophageal junction Siewert type II; G1/G2/G3, tumor grades 1/2/3.

[a]Percentages add to >100% due to concurrent sites of metastatic disease.

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Table 2. Biomarker prioritization and treatment assignment algorithm

Biomarker group and description[a]		Treatment arm	Antibody therapy
1.	IO[b]	Anti–PD-1	Nivolumab
2.	*HER2* amplified[c]	Anti-HER2	Trastuzumab
3.	*EGFR* amplified[c]	Anti-EGFR	ABT-806
4.	*FGFR2* amplified[c]	Anti-FGFR2	Bemarituzumab[d]
5.	*MET* amplified[c]	Anti-MET	None available[e]
6.	MAPK/PIK3CA aberrant	Anti-VEGFR2	Ramucirumab
7.	EGFR expressing	Anti-EGFR	ABT-806
8.	All negative	Anti-VEGFR2	Ramucirumab

Abbreviation: IO, immuno-oncology, including PD-L1 IHC combined positivity score >10, high microsatellite instability, tumor mutation burden >15 mutations/megabase, and/or Epstein–Barr virus positive.
[a]The biomarker profile highest on the priority list is prioritized over others if more than one biomarker is present in a given sample. Metastatic disease site is prioritized over primary tumor site if treatment assignment discordance is observed. If a tumor sample does not fit into any of the seven prioritized groups, then it is assigned to the "all-negative" relegation group 8. If the molecular testing is "quantity insufficient," then the tumor is assigned to the "all-negative" relegation group 8 (see the text for more details).
[b]Group 1 IO is prioritized over group 2 *HER2* amplification only in second line or higher. Group 2 *HER2* amplification is prioritized over IO only in first line.
[c]If RTK genes are coamplified in a given sample, the gene with the highest copy number is prioritized.
[d]One patient of four with *FGFR2*-amplified tumors in first line were able to get access to bemarituzumab plus mFOLFOX6 and treated per protocol and included in ITT. One patient of one who evolved to acquire *FGFR2* amplification after first-line therapy received bemarituzumab in second line, and included in ITT.
[e]Of nine patients enrolled with *MET* amplification, two were able to receive crizotinib (and one of these two patients also received cabozantinib after crizotinib-induced pneumonitis) in later lines, and included in a preplanned mITT analysis.

Cooperative Oncology Group (ECOG) performance status of 2, signet ring cells, and peritoneal disease comprised 9%, 26%, and 38%, respectively, of all patients enrolled. The neutrophil-to-lymphocyte ratio (NLR) was high (poor prognosis) in 69% of the ITT patients. Biomarker profiles were unknown at the time of enrollment and patient tumors were evaluated by the predefined biomarker assessment and treatment assignment algorithm (see Methods; Table 2). The median follow-up time among 13 surviving patients (12, 17.6% of ITT) at the data lock was 27.6 months (interquartile range 24.8–40.5; range, 16.6–57.6). In the ITT group, all 68 (100%) patients received first-line therapy, 53 of 61 (87%) had proceeded to receive second-line therapy, and 25 of 60 (42%) proceeded to receive third-line therapy, with 7, none, and 2 patients still on each line, respectively (Supplementary Table S1). Following PANGEA failure, 8 patients (12%) received fourth-line therapy with 3 patients remaining alive on this line, and no fifth-line or later therapies were received. The number of patients with a successful biopsy and profiling as well as numbers of patients receiving cytotoxic therapy and targeted therapy by line of therapy are shown in Supplementary Tables S2 and S3. Of 68 ITT patients, per treating physician's choice, 28 (41.2%) received mFOLFOX7 (no 5FU bolus) at cycle 1, and the remainder received mFOLFOX6 with 5FU bolus (range, 1–9 cycles with bolus, median 2 cycles with bolus; Supplementary Fig. S1). Through the duration of their treatment, 14 of 68 (20.6%) patients received palliative radiotherapy to the primary tumor as allowed per protocol, all of which were proximal esophagogastric junction tumors (14 of 50, 28%; Supplementary Fig. S1). Notably, 4 of 68 (5.9%) patients developed central nervous system (CNS) disease, of whom 2 had *HER2* amplification, 1 had *EGFR* amplification, and 1 had coamplification of *HER2* and *EGFR*. Therefore, 3 of 16 (18.8%) *HER2*-amplified tumors and 2 of 8 (25%) *EGFR*-amplified tumors developed CNS disease (Supplementary Fig. S1).

Efficacy

The study met its primary efficacy endpoint with 45 (66%; 95% CI, 54%–76%) of 68 ITT patients alive at one year (one-sided $P = 0.0024$ for test of null hypothesis that the survival rate at one year is 50%; Table 3). The mOS was 15.7 months (95% CI, 13.4–17.7) and median time to treatment failure (TTF; $PFS_1 + PFS_2 + PFS_3$) was 13.6 months (95% CI, 11.3–15.8) in the ITT group (Fig. 2A and B), compared with mOS of 9.0 months (95% CI, 4.6–20.3) and median TTF of 7.9 months (95% CI, 3.9–18.8) in the non-ITT group ($P = 0.050$ and $P = 0.084$, respectively). The two-, three-, and five-year survival estimates for the ITT population were 29%, 14%, and 11%, respectively. Among the ITT patients, mOS was 25.8 months (95% CI, 14.1–30.1) in higher-priority biological groups 1–4 (group 5 excluded because none treated with ITT), compared with 13.9 months (95% CI, 11.2–16.7) in lower-priority groups 6–8 ($P = 0.002$, Fig. 2C; see Methods on prioritization; Table 2). Among the ITT patients, mOS was 25.8 months (95% CI, 10.8–43.4) in the HER2-positive group 2, compared with 14.9 months (95% CI 11.6–16.9) in all the remaining HER2-negative groups among the ITT population ($P = 0.011$, Fig. 2D). In the modified ITT (mITT) analysis, the mOS was 16.3 months (95% CI, 13.8–17.9) in the mITT group compared with mOS of 8.8 months (95% CI, 4.1–11.4) in the non-mITT group ($P = 0.009$; Fig. 2E). Among the mITT patients, mOS was 21.2 months (95% CI, 14.1–30.1) in higher-priority groups 1–5, compared with 13.9 months (95% CI 11.2–16.7) in lower-priority groups 6–8 ($P = 0.002$, Fig. 2F). In the ITT group, the median PFS_1 was 8.2 months (95% CI, 7.3–9.6) compared with 6.7 months (95% CI, 2.9–10.6) in the non-ITT group ($P = 0.17$, Fig. 3A). Among the ITT population, 28/61 (46%) changed to second line upon progressive disease on maintenance 5FU plus antibody due

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Table 3. Efficacy outcomes in the PANGEA phase II trial by ITT

	ITT ($n = 68$)	Non-ITT ($n = 12$)
OS[a]		
Events	56 (82%)	11 (92%)
1-year survival rate[b]	66%	33.3%
2-year survival rate	29%	8%
Median survival, months (95% CI)	15.7 (13.4–17.7)	9.0 (4.6–20.3)
Progression-free survival (PFS_1)[a]		
Events	61 (90%)	11 (92%)
Median duration, months (95% CI)	8.2 (7.3–9.6)	6.7 (2.9–10.6)
Overall objective response (ORR_1)		
Patients with measureable disease	54 (79%)	10 (83%)
Best overall response		
Complete response	4 (7.4%)	0 (0%)
Partial response	36 (66.7%)	4 (40%)
Stable disease	13 (24.1%)	3 (30%)
Progressive disease	1 (1.9%)	3 (30%)
Objective response	40/54 (74.1%)	4/10 (40%)
Disease control (measurable)	53/54 (98.1%)	7/10 (70%)
Patient with nonmeasurable disease	14 (21%)	2 (17%)
Stable disease	14 (100%)	2 (100%)
Progressive disease	0 (0%)	0 (0%)
Overall disease control	67/68 (98.5%)	9/12 (75%)

Abbreviations: ITT, intention to treat; PFS_1, first-line progression-free survival; ORR_1, first-line overall objective response rate.
[a]Median follow-up among survivors was 27.6 months (interquartile range, 24.8–40.5; range, 16.6–57.6)
[b]The primary efficacy endpoint was 1-year survival rate.

to persistent neuropathy (26/61) or prior oxaliplatin allergic reaction (2/61), precluding resumption of oxaliplatin, whereas the remaining patients experienced progressive disease while receiving FOLFOX plus antibody therapy. Among the ITT population having evaluable disease by RECIST1.1, the disease control rate in first-line (DCR_1) was 98.5% (67/68) and the first-line objective response rate (ORR_1) among the 54 patients with measurable disease was 74.1% (40/54; Fig. 3B; Supplementary Fig. S2A). Results of all endpoints by treatment line and biological subgroup, as well as mITT, are summarized in Supplementary Fig. S2B–S2G and Supplementary Tables S4 and S5.

Biomarker Spatial and Temporal Heterogeneity

Among the 80 patients enrolled, the baseline incidence of each biomarker generally represented the incidences as determined in larger sample sets (Fig. 4A; Supplementary Table S6; refs. 4, 29, 30). However, comparison of the baseline primary versus metastatic tumor molecular profiles demonstrated 28 of 80 (35%) patients having discordant treatment assignments based on the biomarker assignment and treatment algorithm. This baseline discordance led to higher incidence of some biomarker groups, particularly *FGFR2* and *MET* amplifications, due to directional (primary to metastasis) acquisition of these aberrations (Fig. 4A). The incidence of patients assigned to immuno-oncologic (IO) by the metastatic site using the combined positivity scoring (CPS) ≥10 cutoff was 5/80 (6.3%, one of which was MSI-high); using a lower cutoff of CPS ≥5 would have added 5 more patients (10/80 or 13% total). Remarkably, the incidence of patients assigned to group 1 IO due to either EBV^+ or tumor mutation burden (TMB)–high (≥15 mt/MB) was 0% in the 80 patients evaluated at baseline, other than 1 patient with an MSI-high tumor that was TMB-high (24 mt/MB). Two of 80 patients did have TMB-high primary tumors but TMB-low metastatic tumors; 1 of these patients was still assigned to group 1 IO per the protocol/algorithm because both lesions were very high PD-L1-expressing (CPS 100 primary tumor and CPS 95 metastasis). In 19 of 80 (23.8%) patients, HER2 positivity was noted in either the primary tumor and/or the metastatic tumor. Of these, 16 (20%) had HER2 positivity and the highest gene copy if there were concurrent RTK amplifications in the metastatic site, and therefore were assigned to the HER2 group per the protocol/algorithm (Supplementary Table S7). Notably, *HER2*-amplified primary tumors were not amplified in their paired metastases in 2 patients, whereas *HER2*-nonamplified primary tumors were amplified in metastases in 2 other patients, resulting in a net zero change in incidence, but a change in treatment for 4 patients. Additionally, 1 patient had concurrent *EGFR* and *HER2* amplification, with a higher *EGFR* copy in both the primary tumor and metastatic biopsies, leading to concordant assignment to group 3 *EGFR* amplification per the biomarker assignment algorithm (Table 2), but against current standard treatment guidelines. Therefore, 3 of 17 (17.6%) *HER2*-amplified primary tumors were assigned to different groups (2 patients to group 3 *EGFR* amplification, 1 patient to group 5 *MET* amplification), and 2 of 63 (3.2%) *HER2*-nonamplified primary tumors were

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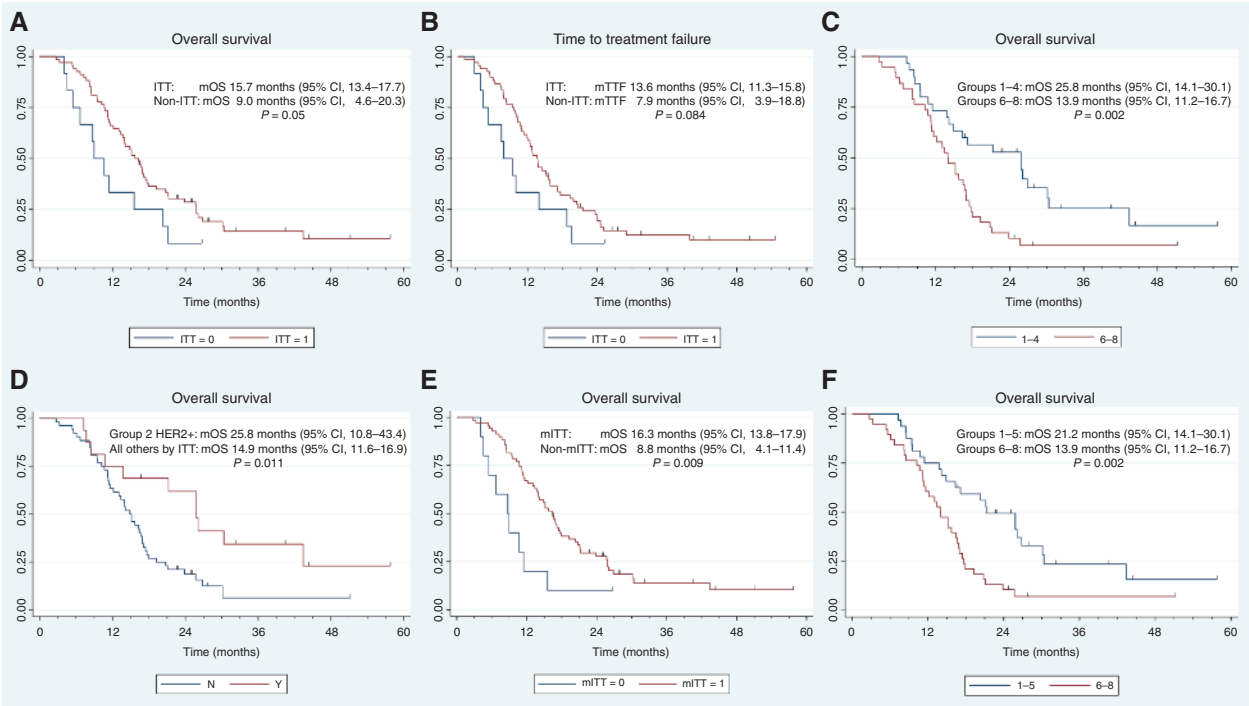

Figure 2. **A,** OS in the ITT group (red) versus the non-ITT group (blue). **B,** The time to PANGEA treatment failure in the ITT group versus the non-ITT group. **C,** OS comparing higher-priority biomarker groups 1–4 (blue) to lower-priority groups 6–8 (red) among the ITT population (no group 5 patient treated with ITT). **D,** The OS comparing the HER2$^+$ group (red) versus the HER2$^-$ group (blue) among the ITT population. **E,** The OS in the modified (mITT) group (red) versus the non-mITT group (blue). **F,** OS comparing higher-priority biomarker groups 1–5 (blue) to lower-priority groups 6–8 (red) among the mITT population.

assigned to group 2 *HER2*-amplified based on the algorithm's predefined rules.

Temporal molecular heterogeneity is captured in the swimmer plot demonstrating TTF over up to three lines of therapy (Fig. 4B; Supplementary Fig. S1). Among mITT patients progressing on first-line therapy with evaluable tumor samples at first progression (PD1), comparison of the first biomarker group assignment to the second group assignment demonstrated a group assignment change in 27 of 55 patients (49%; Fig. 4B; Supplementary Tables S2 and S3). Of mITT patients progressing on second-line therapy with evaluable tumor samples at PD2, comparison of the third group assignment to the previous assignment demonstrated a group change in 13 of 27 (48%) patients. Of 16 patients initially assigned to the *HER2*-amplified group, 3 remained on first-line therapy at the data cutoff, and 2 progressed with CNS disease and were unable to obtain PD1 biopsies. Of the remaining 11 initially *HER2*-amplified patients, 4 (37%) evolved to other groups at PD1 (2 to IO group 1, and 2 to MAPK/PIKC3A aberrant group 6). Similarly, 4 of 6 (67%) *HER2*-amplified second-line patients evaluable at PD2 evolved to other groups (2 to IO group 1, 2 to MAPK/PIKC3A aberrant group 6), for a total of 8 (72.7%) evolving at either PD1 or PD2 to *HER2*-nonamplified groups. However, all 4 patients evolving to the IO group 1 retained *HER2* amplification but were prioritized per the algorithm rules, leaving 4 of 11 (45.5%) actually having *HER2*-nonamplified tumors. Of these 4 patients converting to *HER2*-nonamplified tumors, 1 (25%) had resurgence of *HER2*-amplified disease at PD3. Notably, although only 5 of 80 (6.25%) patients were assigned to the IO group initially, 10 of 65 (15.4%) patients who were exposed to any targeted therapy in the mITT group, including the 4 *HER2*-amplified ones noted above, evolved to group 1 IO in either the second or third line, but only 6 of those 10 patients received IO therapy on study, because the other 4 patients had progressive disease and died before being able to implement it. Specifically, PD-L1 conversion occurred in 7 of 27 (26%) RTK-amplified tumors after exposure to RTK targeted therapies. In contrast, none of the 10 patients in the non-mITT group (all RTK-amplified tumors but not receiving targeted therapies) changed to IO at later lines. Through the study duration over up to three therapy lines, 15 of 70 (21.4%) patients were assigned to IO at least once, and 11 of 70 (15.7%) patients were able to receive it.

Among the 14 esophagogastric junction patients requiring radiotherapy to the primary tumor for symptomatic dysphagia and/or bleeding, each had systemic disease controlled at the time. Of the 9 of these patients on non-IO therapy with evaluable NGS testing of the primary tumor just prior to radiotherapy, 8 (88.9%) of the sampled tumors had acquired new genomic alterations and/or loss of the intended target of their assigned biological group.

Safety and Feasibility

There were no diagnostic or treatment-related deaths. Of 327 biopsies (156 primary tumors; 171 metastatic tumors) obtained at baseline and through three lines of therapy, 1 patient (<1%) was admitted overnight for monitoring due to abdominal pain after baseline ultrasound-guided biopsy of a peritoneal nodule, then discharged the next day; thus,

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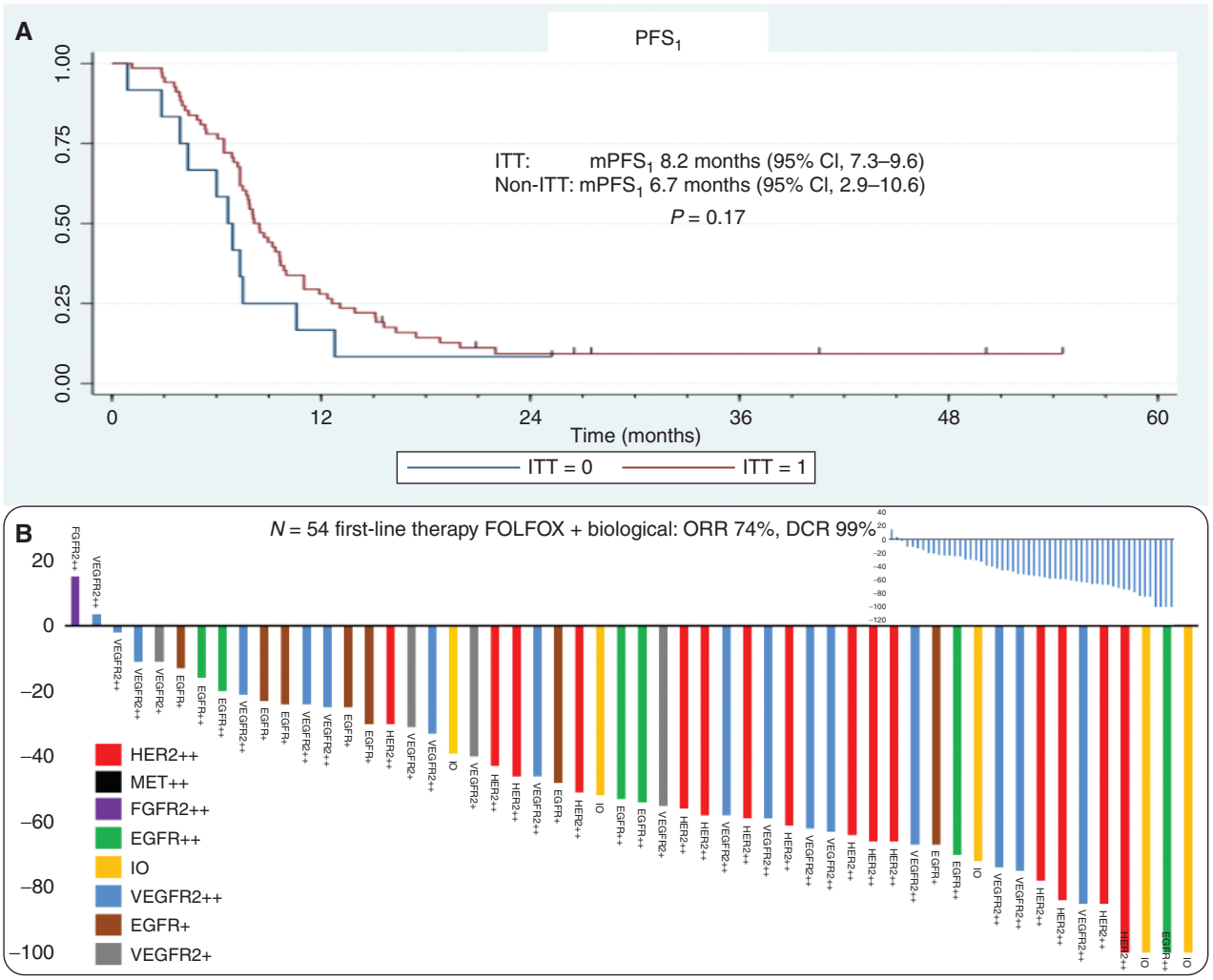

Figure 3. **A,** The first-line progression-free survival (PFS_1) in the ITT group (red) versus the non-ITT group (blue). **B,** Rainbow waterfall plot demonstrating objective response rate (ORR_1, 74%) and disease control rate (DCR_1, 99%) by molecular group to first-line cytotoxic therapy plus matched monoclonal antibody among patients within the ITT population who had baseline measurable disease ($N = 54/68$). Inset, waterfall plot for ORR_1 ITT treated per protocol.

the diagnostic approach was deemed safe. Of 80 patients enrolled, 77 (96%) were successfully assigned by the treatment algorithm within two months, meeting this feasibility endpoint. Among 72 patients progressing on first-line therapy, 60 (83%) had PD1 biopsies successfully [51 of 61 (84%) ITT; Supplementary Table S2]. Of 60 patients actually proceeding to receive second-line therapy, 55 (92%) obtained PD1 biopsies successfully [49 of 53 (92%) ITT], meeting this feasibility endpoint. Of 28 patients proceeding to third-line therapy, 24 (86%) had PD2 biopsies successfully [21 of 25 (84%) ITT].

Grade 3 or higher treatment-related adverse events through all three treatment lines are reported in Table 4, with the most common being cytopenias, fatigue, nausea, and vomiting, each attributed to the cytotoxic therapy and not the monoclonal antibodies. The most common dose modification was stopping the 5FU bolus. Grade 3 treatment-related adverse events attributed solely to monoclonal antibodies were reported in 2 patients, including 1 patient with ramucirumab causing nephrotic syndrome and 1 patient on bemarituzumab causing corneal keratitis, reported elsewhere (31).

DISCUSSION

In this patient-centric phase II study for newly diagnosed advanced GEA, a novel study design was implemented to test an individualized treatment strategy using monoclonal antibodies matched to tumor molecular profiles in combination with chemotherapy for up to three lines of sequential treatment (16, 21, 22, 27, 28). The study reached its primary endpoint, with 45 of 68 patients (66%) alive at 12 months, per ITT, exceeding the 50% historical control rate. The mOS of 15.7 months, the DCR_1 of 98.5%, and the ORR_1 of 74.1% are each substantially numerically higher than would be expected if treating with standard first-line therapy. A better outcome than expected was observed even for the HER2-positive subgroup, with a median OS of 25.8 months compared with HER2-positive historical controls of 14 to 16 months (3, 32).

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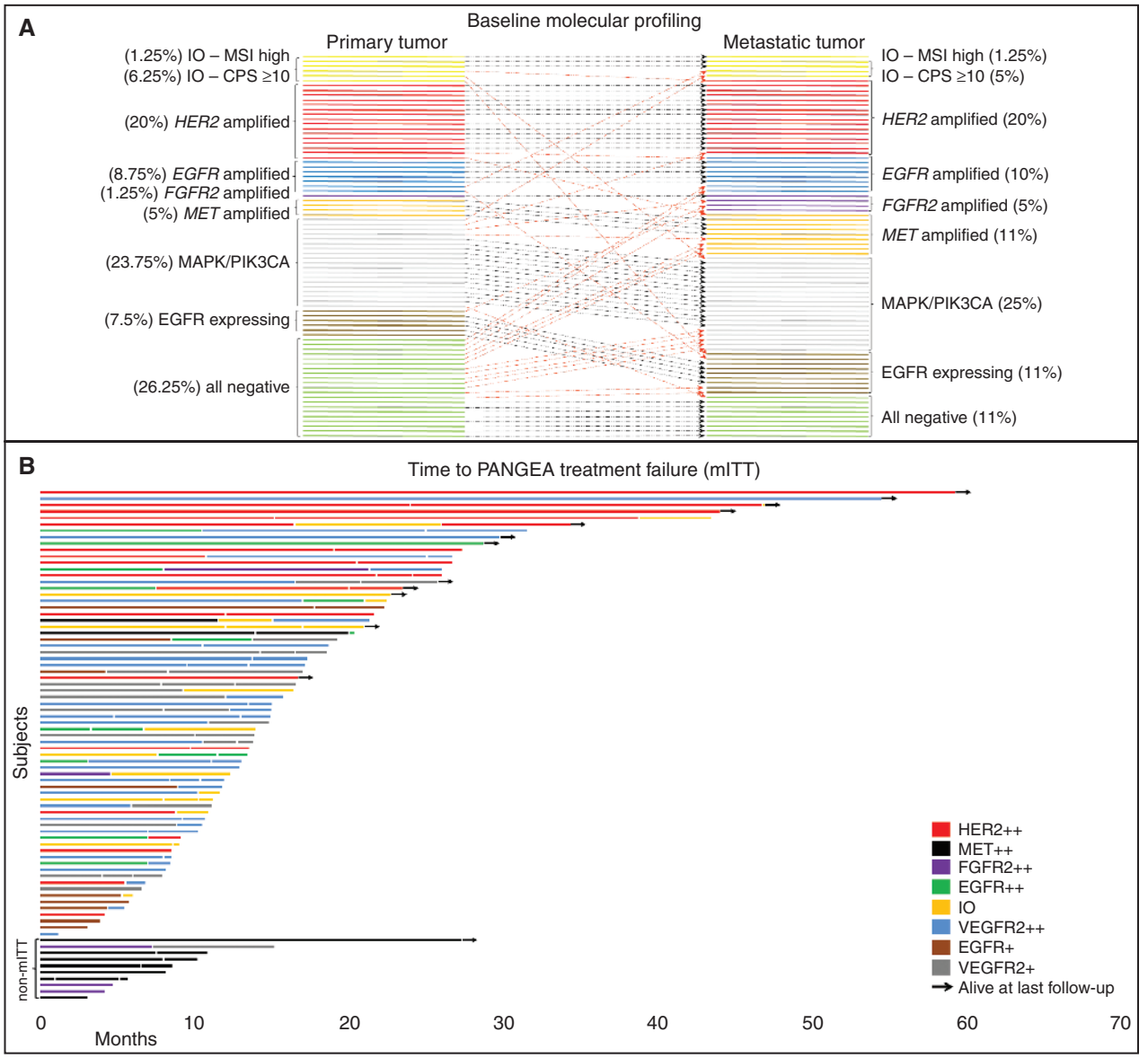

Figure 4. **A,** Comparison of the baseline primary versus metastatic tumor molecular profiles in each of 80 enrolled patients, demonstrating concordant (black) or discordant (red) biomarker assignments. IO, Immuno-oncology, group 1; CPS, combined positivity score; *HER2* amplified, group 2; *EGFR* amplified, group 3; *FGFR2* amplified, group 4; *MET* amplified, group 5; MAPK/PIK3CA or "KRAS-like," group 6; all negative but EGFR expressing by mass spectrometry, group 7; all negative or quantity insufficient, group 8. See Table 2 for details on biomarker assignment and treatment algorithm prioritization rules. **B,** Rainbow swimmer plot including up to three lines of therapy by modified ITT (mITT) group (top) versus non-mITT group (bottom). Temporal molecular heterogeneity is captured for each patient by colored bars indicating treatment group assignment at each treatment line for up to three lines of therapy.

The biomarker testing strategy was deemed feasible and safe, as previously described (33), including in the many patients treated with ramucirumab without any breaks in biweekly dosing for biopsies. The high rate of post-treatment biopsies on this study is likely due to patient willingness given the direct impact on their own next-line treatment. Also, treatment-related toxicities were similar to and even better than those reported for standard cytotoxic therapy, where almost half of patients received mFOLFOX7 and all received mFOLFIRI (no 5FU bolus in either regimen). Given the exceptional efficacy observed in this study, this suggests that the utility of 5FU bolus is limited, and it is our routine practice not to include it in most patients. Moreover, the use of novel combinations of the three chemotherapy backbones and the six monoclonal antibodies in the study resulted in no new safety concerns. It is also the first study, to our knowledge, to study anti–PD-1 therapy beyond progression in persistently PD-L1–positive (CPS > 10) tumors. The results suggest that the addition of a matched targeted monoclonal antibody at each of up to three time points, directed toward the predominant tumor biology at any given time point, is safe and feasible in patients with advanced GEA, and led to improved efficacy over historical controls.

The incidence of each biomarker subgroup enrolled did approximate what would be anticipated within GEA as a

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Table 4. Grade 3 or higher treatment-related adverse events over three treatment lines and by treatment line

Event	All lines ($n = 68$)	1L ($n = 68$)	2L ($n = 53$)	3L ($n = 25$)
Adverse event				
Fatigue	9 (13%)	3 (4%)	3 (6%)	4 (16%)
Anorexia	1 (1%)	—	1 (2%)	—
Infection	3 (4%)	2 (3%)	1 (2%)	—
Nausea/vomiting	6 (9%)	4 (6%)	2 (4%)	—
Diarrhea	3 (4%)	—	3 (6%)	—
Hematologic toxicity				
Neutropenia	12 (18%)	6 (9%)	4 (8%)	3 (12%)
Anemia	11 (16%)	7 (10%)	2 (4%)	3 (12%)
WBC decreased	6 (9%)	1 (1%)	2 (4%)	3 (12%)
Thrombocytopenia	4 (6%)	4 (6%)	—	—

Abbreviations: 1L, first line; 2L, second line; 3L, third line.

whole (4, 29, 30), and therefore, as intended, the results observed are representative and generalizable. In larger confirmatory studies using this trial design, the incidences of the biomarker groups would also be expected to approximate the actual incidences within the disease because the nature of the study is to enroll all comers. However, it is important to acknowledge that due to the inevitable overlap of biomarkers within a given tumor sample and between primary tumor and metastatic sites, the prioritization scheme would inherently then favor certain biomarker groups over others, leading to somewhat distorted biomarker group and treatment assignment incidences. For instance, the actual IO group 1 incidence at diagnosis was lower than would be expected using CPS ≥ 10, and can be attributed both to the prioritized assignment to *HER2* amplification, despite some of these tumors also harboring high PD-L1 expression and/or high TMB, and to other cases where conversion to PD-L1–negative or TMB-low was observed in the baseline metastatic biopsy, which took priority when there was observed primary/metastasis discordance. The degree of spatial intrapatient heterogeneity of PD-L1 and TMB within GEA was recently reported, emphasizing directional discordance from positive primary tumors to negative metastatic lesions (34).

The reasoning to devise a structured biomarker testing and treatment assignment algorithm was to ensure that outcomes could be reproducible by others, rather than the *ad hoc* and sometimes spontaneous treatment decisions currently made in the "precision medicine" clinic today, especially when there is more than one option from which to choose. The rationale of the specific biomarker groups chosen and their detailed prioritization within the algorithm was based on preclinical and clinical evidence available at the time of designing this study several years ago. Notably, these groups each remain potential targets not yet routinely implemented for first-line and/or later-line therapy to date, despite numerous studies attempting to do so using classic study designs (6–11, 14, 15, 35–49). An important recent example is the FIGHT study evaluating the anti-FGFR2 antibody bemarituzumab for *FGFR2*-amplified tumors. The study was originally a phase III study, but given *FGFR2* amplification biomarker incidence of only ~5% of GEA and an unclear optimal IHC biomarker cutoff, it was downsized to a phase II study in part due to accrual infeasibility for this rare but important genomic subset (https://investor.fiveprime.com/news-releases/news-release-details/five-prime-therapeutics-reports-first-quarter-2020-results; ref. 36). However, relevant drug approvals did occur during the conduct of this PANGEA study, including the anti-VEGFR2 antibody ramucirumab alone or in combination with chemotherapy in the second-line setting (50, 51), and the anti–PD-1 antibody pembrolizumab for MSI-H tumors in the second line (52, 53), and for PD-L1 CPS ≥ 1 tumors in the third line (54). Also in the interim, studies of ramucirumab antiangiogenesis in the first line were negative for mOS, despite improvements in ORR and PFS, adding to prior negative studies with bevacizumab (14, 15, 42, 55). Trifludirine/tipuracil, an oral cytotoxic agent, also demonstrated improved survival in the third-line setting or higher (56); notably, no patients were treated with this agent during the study or afterward in fourth line or higher. Additionally, despite the fact that during the conduct of our study, several first-, second-, and third-line studies demonstrated negative results for unselected and selected patients with anti–PD-1/L1 therapies (44–49), two first-line GEA studies, KEYNOTE-590 and Checkmate-649, recently showed improvement in mOS, most notably in subsets of patients with PD-L1 CPS ≥ 10 or CPS ≥ 5, respectively (57, 58). It is interesting to note that the IO group in our study, defined by either of these PD-L1 CPS thresholds, was substantially lower in incidence than these studies, whereas the mOS of these patients was 16.2 months in our study compared with 14.4 months (14 months in non-Asians) in the Checkmate-649 study (58). This is potentially due to the higher PD-L1 cutoff of CPS ≥ 10 versus CPS ≥ 5 better enriching for more benefit, due to targeting the metastatic tumor, and/or due to continued therapeutic matching over sequential therapies. Further studies will need to define the optimal PD-L1 cutoff and sample site to assess (34). A key advantage of the type II expansion-platform design is the need for far fewer patients, and therefore less time and resources, to arrive at the same answer compared with a large study such as Checkmate-649 with ~1,600 patients.

Notwithstanding results of these interim IO studies reporting during or after the conduct of our study, we continued the PANGEA study as designed, because its logic dictated

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that the patient would be matched with the monoclonal antibody best suited for them at any given time through their treatment course. If a tumor did not possess relevant biomarkers to predict benefit of a given targeted therapy, then the patient was not treated with that therapy, irrespective of whether or not it was approved for that treatment line. Moreover, despite the perceived negative first-line antiangiogenesis studies that demonstrated improved PFS, ORR, and trends to OS (14, 42), the PANGEA strategy continued to match antiangiogenesis to lower-priority arms in the first and later lines if it was the best available option, because it was hypothesized that some benefit (HR ~0.8–0.85) could still be realized relative to chemotherapy alone, thus contributing to the overall favorable ITT outcome. Consistent with the hypothesis, although the lower-tier groups experienced worse outcome compared with higher-tier groups within the PANGEA algorithm as was anticipated, they still fared better than would be expected when compared with historical controls. In fact, the patients assigned to antiangiogenesis therapy in the first line, of whom most tended to remain in these groups (groups 6 and 8) over subsequent lines, achieved excellent one-year OS of 62% to 67% and mOS of 14 to 15.1 months. Indeed, if a study was conducted with ~1,600 patients, such as Checkmate-649, with an antiangiogenesis agent for first-line therapy, this would be larger than the combined phase III studies of both AVAGAST with bevacizumab (N = 774) and RAINFALL with ramucirumab (N = 645; refs. 14, 54), with more power to detect this smaller but real difference in survival. This has also been demonstrated for first-line colorectal cancer in a pooled analysis of seven trials with >3,750 patients (59). Additionally, among these tumors lacking better targeted therapeutic options, the improved outcomes observed may in particular be attributed to the continuation of antiangiogenesis beyond progression, similar to that experienced with colorectal (60), hepatocellular (61), breast (62), and other cancers (63).

The PANGEA logic did not spare those who would be considered HER2-positive clinically based on the primary tumor alone, because per protocol if there was spatial heterogeneity, the metastatic site would dictate treatment assignment, with the rationale that metastases are the ultimate drivers of poor outcome. For the cases having baseline HER2-positive primary tumors but HER2-negative metastatic lesions, some tumors at PD1 or PD2 eventually did demonstrate HER2 positivity in progressing lesions, whereby patients then received trastuzumab at that time. In contrast, other such cases at PD1 or PD2 remained HER2-negative in progressing lesions despite persistently HER2-positive primary tumors, and thus trastuzumab was never used per the algorithm. Interestingly, of these cases with HER2-positive primary tumors having never received trastuzumab, none required palliative radiotherapy to the primary tumor. Also, some cases that were HER2-negative in the primary tumor were HER2-positive at the metastatic site, whereby they would not have otherwise received anti-HER2 therapy without intentionally evaluating the metastatic disease burden. Indeed, this was the rationale for including "HER2-positive" and "HER2-negative" tumors within the same study—because there is often an interplay between these groups within the same patient. Furthermore, this is the first study to our knowledge to prospectively address baseline spatial and temporal heterogeneity for HER2-positive disease, and may account for the extremely good outcome observed in this group. Trastuzumab beyond progression with alternate chemotherapy backbones, in the appropriately selected patients, appeared very active and also safe. Thus, compared with this and other readily available anti-HER2 strategies, the benefit of the recently reported anti-HER2 antibody–drug conjugate trastuzumab–deruxtecan must be weighed against the higher clinical and financial toxicity that comes with it, should it indeed demonstrate activity in Western populations similar to that it has in Asia (64).

The improved clinical outcomes observed across the ITT group and subgroups in this study, including the HER2 group, support the strategy of assessing the main problematic component of the disease at any given time point and targeting it therapeutically in a prioritized manner. With this strategy, it was common for systemic disease to be well controlled, but with an eventual local progression from the primary tumor requiring palliative radiotherapy. This occurred in 14 (20.6%) patients, or 28% of proximal esophagogastric junction disease. This occurred more than 10 months from diagnosis in half of these cases. In 89% of these cases with available tumor just prior to radiotherapy, the primary tumor had either lost the intended biological target (e.g., loss of *HER2* or *EGFR* amplification) and/or acquired other likely resistance mechanisms such as other concurrent RTK amplifications and/or *KRAS* aberrations (29, 40, 65), phenomena also reported in the interim by others (66, 67). After completion of radiotherapy, each patient resumed the previous systemic therapy until systemic disease progression. Additionally, despite brain metastases being infrequent for GEA (68), the CNS served as a sanctuary site in an extraordinarily high percentage of *HER2*- and *EGFR*-amplified tumors, consistent with previous reports (69). With better control of systemic disease using targeted approaches, this will likely become more common, as seen in other tumors (69, 70).

Biomarker heterogeneity was prevalent, both spatially at baseline and sequentially over each treatment line. Notably, this was a conservative analysis, only considering molecular discordance spatially and temporally if a treatment assignment was changed per the algorithm. However, metastatic and later-line tumors commonly remained within the same treatment assignment yet harbored additional molecular aberrations compared with the baseline primary tumor. Common examples of this were among RTK-amplified tumors where acquired *KRAS* mutations and/or amplifications were observed in addition to the original RTK amplification (65). Here, per the algorithm used in this study, tumors would still be classified as the same baseline RTK-amplified tumor despite these acquired genomic events. Future studies could test alternative postprogression algorithms (16).

Regardless, using this conservative molecular heterogeneity estimate of the PANGEA algorithm, an interim evaluation of baseline spatial heterogeneity after 28 patients enrolled previously reported 9 of 28 (32%) patients receiving a different therapy by the metastatic profile compared with the primary profile (71). Herein, we report the final baseline spatial heterogeneity leading to altered treatment assignment in 28 of 80 (35%) patients enrolled. Additionally, substantial temporal biomarker evolution led to treatment change at the

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time of changing to second-line (49%) and third-line (48%) therapies. In contrast, those patients with *FGFR2* or *MET* amplification at diagnosis mostly retained this designation throughout their course of therapy when treated with chemotherapy alone. However, both patients with *FGFR2* amplification and both patients with *MET* amplification within the modified-ITT group, after exposure to respective targeted therapies, evolved to different biomarker groups at the time of progression. This suggests that imposing pressure on the biological target, though leading to improved clinical outcomes, will ultimately force evolutionary change and drive eventual resistance, often through selection of biomarker-negative clones, whereas chemotherapy alone generally will not. Observed mechanistic resistance in the mITT population occurred through various means, often through selection of RTK-negative clones, downstream MAPK/PIKCA aberrations, and/or upregulation of PD-L1 expression. The latter phenomenon of PD-L1 upregulation, as recently reported by our group (34) and others (72), occurred in 7 of 28 (25%) patients harboring RTK-amplified tumors and exposed to RTK-targeted therapies, supporting future dual anti-RTK antibody plus anti–PD-1 antibody approaches in order to enhance simultaneous innate and acquired immune activity, respectively (23, 24, 43, 73, 74).

There are limitations to this study. The first is the lack of a randomized control arm and its conduct at a single academic center, each leading to potential selection bias. However, the study was intended to demonstrate the feasibility, safety, and proof of principle of this novel approach. Also, patients were enrolled with baseline high-risk features including 38% with peritoneal disease, 9% with ECOG performance status of 2, and 70% of patients with high baseline NLRs, indicating poor prognosis (75). Patients also consented, screened, enrolled if eligible, and, per protocol, then immediately initiated first-line palliative cytotoxic therapy while awaiting biomarker testing (as opposed to waiting for molecular testing during a screening period while not receiving any therapy until receipt of the results). These factors suggest that the patients enrolled on PANGEA were not enriched for better prognoses (e.g., those who could afford to await biomarker testing results before initiating therapy), and indeed some patients enrolled here would not be candidates for typical phase II or III biomarker-selected studies. The study also accrued at two community satellite sites with a number of treating investigators. All of these points make the findings of this real-world patient population more generalizable, yet still requiring further prospective randomized and multicenter prospective validation.

The second limitation is the lack of power to evaluate each biomarker subgroup. This is an inherent limitation of the expansion-platform type II design, and a recognized concession in order to confront the problem of difficult-to-study low-incidence biomarker groups as well as the sequential profiling and matching through later lines of therapy where subgroups get divided even further by various mechanisms of resistance (16, 21). Low-incidence biomarker groups remain challenging to study (20, 76). Isolated prospective evaluations of each component of the PANGEA strategy individually often either have been attempted and overall found negative or have been prohibitive and infeasible to conduct (https://investor.fiveprime.com/news-releases/news-release-details/five-prime-therapeutics-reports-first-quarter-2020-results; ref. 39). The hypothesis tested here evaluated whether the strategy together could overcome these hurdles. However, to demonstrate that no one "supergroup" could sway the result, preplanned analyses first excluding the *HER2*-amplified group and second excluding all higher-priority genomically targeted groups 1–4 (IO, HER2, EGFR, and FGFR2) showed that the remaining groups still experienced improved outcomes, to the degree that would be expected, compared with historical controls. Group 7, however, which was EGFR-overexpressing tumors treated with an anti-EGFR antibody after excluding higher-priority groups as well as group 6 MAPK/PIK3CA-driven tumors, did apparently underperform. Although it cannot be excluded due to lack of a randomized control that this group may have a worse natural prognosis that might still have benefited from anti-EGFR therapy (or due to low numbers and lack of power to identify a true benefit), this group would not proceed into future iterations of the personalized strategy.

Third, we were unable to secure collaboration to obtain anti-FGFR2 or anti-MET antibodies. As a consequence, given that each of these biomarkers is notably associated with poor prognoses (36, 77), this may partially explain the worse outcomes of the non-ITT group, and also therefore does not necessarily represent the whole of GEA as a historical control. However, we were able to get access through a parallel open-label phase Ib study for the anti-FGFR2 antibody bemarituzumab (31, 36), plus modified FOLFOX6 for 2 patients in the FGFR2 group 4 who were treated per protocol and included in the ITT analyses. Additionally, we were able to obtain off-label MET small-molecule inhibitors as monotherapy for 2 patients in the MET group 5, and these were analyzed in a preplanned mITT analysis that showed an even better mOS of 16.3 months when including these patients treated with a "PANGEA-like" strategy compared with the remaining non-mITT group. Next-generation regulation to recognize type II expansion-platform studies such as PANGEA to encourage pharmaceutical company participation will be important for the future success of moving personalized treatment strategies forward. Smaller companies, not able to conduct large 1,600+ patient studies, would benefit from this significantly. To facilitate and encourage innovation, one might envision an accelerated conditional approval pathway, akin to those already in place for novel therapies based on therapeutic response rates, for each component of a prospectively tested personalized treatment strategy. Indeed, novel neoantigen vaccines entering the clinic are the epitome of the expansion-platform type II design, with each patient having the same diagnostics and treatment platform/algorithm, but with a uniquely engineered therapeutic vaccine specific to only their tumor—a true "N-of-1" personalized approach (78). Of note, one randomized expansion-platform type II study was reported in the interim since we initiated our study (79). Although the utility of its prespecified treatment strategy was refuted by the results, the SHIVA study tested a treatment strategy prospectively and introduced the uncertainty surrounding regulatory approvals of multiple diagnostics and therapies simultaneously if such a study was positive (21).

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Finally, the evaluation of secondary endpoints, such as $ORR_{2,3}$, $PFS_{2,3}$, and $DCR_{2,3}$, in later lines of therapy was limited by lower power due to many patients not proceeding to these treatment lines due to either remaining on earlier lines at the time of data cuts or inability to proceed due to progressive clinical deterioration. Also, many patients with clinical progressions did not have RECISTv1.1 measurable disease after such high ORR_1 (74%) with deep responses, but were still evaluable and contributed to high DCR_2 (72%) and DCR_3 (68%). Importantly, in comparison with a dedicated standalone second- or third-line study capturing all types of patients proceeding to next-line therapy (e.g., quick progressors and late progressors), the patients on this study who would proceed to later lines at any data cut would represent those patients with more aggressive tumors compared with those remaining on earlier lines, and thus would impose a negative selection bias for later-line secondary analyses. The criteria for treating in second or third line on PANGEA were also less stringent and more practical than would otherwise be routinely imposed at screening for typical late-line studies. As a consequence, although a higher than expected 87% and 42% of patients proceeded to second-line and third-line therapy, respectively, 15% and 44% of those did not receive intended new targeted agents because they deteriorated clinically prior to our being able to identify and implement them. Despite this drop-off of successful matching, these patients were included within all ITT analyses. As such these factors should be considered when comparing these later-line secondary endpoints from PANGEA with other independent later-line studies. Relevantly, another possibility to explain the higher rates of later-line therapy may be that the PANGEA approach alters the biology of the cancer, making patients more likely to proceed to later lines, which requires further exploration.

This study evaluated the utility of optimizing the chemotherapy sequence, the biomarker profiling, and the matching of molecular therapies at baseline and over time, which resulted in improved outcomes compared with historical controls for newly diagnosed metastatic GEA. However, despite these advances, hypotheses are formed on how to further improve on these outcomes. The therapeutic resistance observed, which generally converged on common pathways and mechanisms, suggests that preemptive dual targeted inhibition may lead to even further progress, such as combined RTK inhibition for concurrent RTK-amplified tumors (40, 80, 81), IO and antiangiogenesis (82, 83), or a combination of IO and RTK inhibition (40, 43, 73, 74, 84), in a similarly prioritized manner. The results of PANGEA support the prospective comparison of such personalized treatment strategies in a randomized controlled trial.

METHODS

Study Design and Participants

This study was an investigator-initiated, phase II, open-label, single-arm type II expansion-platform trial (16, 21, 22) performed at The University of Chicago along with two of its community-based satellite sites. The study protocol and all amendments were approved by The University of Chicago institutional review board. The protocol was conducted in accordance with the Declaration of Helsinki and was overseen by an internal data and safety monitoring committee. All patients provided written informed consent before enrollment.

Eligible patients were ages 18 years or older with histologically proven metastatic GEA from a biopsy of a stage IV site (cytology was acceptable from effusions/ascites). Patients were required to have newly diagnosed advanced disease, or recurrence after previous curative-intent therapy if completed more than six months prior. Key inclusion criteria included ECOG performance status of 0 to 2, and no grade 2 or higher peripheral edema, peripheral neuropathy, or diarrhea. Patients had measurable or evaluable nonmeasurable disease as per RECISTv1.1. Key exclusion criteria included history of known or suspected autoimmune disease, active second malignancy, intercurrent illness/infection, cardiac ejection fraction less than 50%, or history of cerebral vascular accident or myocardial infarction within six months. Full eligibility details are in the protocol (see Appendix in the supplementary files).

Biomarker Assessment and Prioritized Treatment Assignment

Biomarker profiling assays were performed in parallel on all samples, including baseline primary and metastatic biopsies, as well as first (PD1) and second (PD2) progressive disease biopsies. Analyses included NGS using FoundationOne, including MSI and TMB testing (85), along with CPS of PD-L1 by IHC using the 22C3 pharmDx assay (86), all from Foundation Medicine. PD-L1 was considered positive at CPS ≥10, and TMB was high if ≥15 mutations per megabase (34). Genes were considered amplified by NGS if eight copies or higher were observed. HER2 status was assessed and considered positive if $IHC3^+$ or $IHC2^+$ together with FISH amplification (ratio of *HER2*:*CEP17* probes greater than or equal to 2; ref. 87). Circulating tumor DNA (ctDNA) was obtained and analyzed using Guardant360 at baseline and serially at each disease progression time point, as previously described (29, 88). If *EGFR* or *MET* amplification was identified in one of a patient's tissue- or ctDNA-NGS results, all of that patient's samples were analyzed for these two genes by FISH at Neogenomics (40). If a sample demonstrated PD-L1 CPS ≥ 10 and was not MSI-H, then Epstein–Barr virus (EBV) status was determined by ISH using probes against Epstein–Barr encoded RNA1. EGFR expression by selected-reaction-monitoring mass spectrometry (SRM-MS) was quantified and considered positive if above the limit of detection (attomols/microgram), as previously described (40, 89). To address the possibility of insufficient tissue to perform all intended analyses, testing was prioritized on each sample by a set of rules in accordance with the treatment assignment algorithm described below.

Based on the results of this extensive molecular profiling, a tumor sample was assigned to one of eight biological categories based on a predefined algorithm (Table 2): Group 1 IO, including MSI-H, EBV+, TMB high [≥15 mutations/megabase (mt/Mb)], and/or PD-L1 IHC CPS ≥10; groups 2–5 RTK amplification of *HER2, EGFR, FGFR2,* and *MET*, respectively; group 6 genomic activation of the MAPK/PIK3CA/GNAS pathways; group 7 EGFR expressing by SRM-MS; group 8 all negative. The group 1 IO was prioritized second to group 2 HER2-positive tumors in the first-line setting only, but was then first priority in second line and later. For groups 2–5, if two or more RTKs were concurrently amplified, then the gene with the highest copy number would take priority, given evidence that higher gene copies correlated with higher expression, which correlated with higher efficacy of matched targeted therapy (3, 29, 40, 90–93). If the final biomarker assignment was discordant between the primary and metastatic tumors at baseline prior to first-line therapy, then the metastatic tumor would take precedence. If the quantity of metastatic tissue was not sufficient (QNS) to complete all assays and biomarker assignment, then ctDNA could be used for biomarker assignment. If there were no alterations actionable by ctDNA per the algorithm, then the primary tumor profile was used. If QNS despite these steps, then the patient would be assigned

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to group 8. Temporal (PD1, PD2, and PD3) biopsies were obtained from progressing lesions.

Therapeutic Procedures

Cytotoxic doublets were administered as biweekly treatment cycles in each of up to three therapy lines (Supplementary Fig. S3). First-line cytotoxic therapy of modified FOLFOX6 entailed day 1 oxaliplatin 85 mg/m^2 i.v. with leucovorin 200 mg/m^2 i.v. over 2 hours, then 5-fluorouracil (5FU) bolus 400 mg/m^2 i.v., then 2,400 mg/m^2 i.v. continuous infusion over 46 hours. An 8/2016 amendment permitted, at the discretion of the treating investigator, omission of the 5FU bolus and leucovorin from the onset of treatment (modified FOLFOX7). Second-line cytotoxic therapy of modified FOLFIRI (no 5FU bolus) entailed irinotecan 180 mg/m^2 i.v. with leucovorin 200 mg/m^2 i.v. over 2 hours, then 5FU 2,400 mg/m^2 over 46 hours. Third-line cytotoxic therapy of FOLFTAX entailed docetaxel 50 mg/m^2 i.v. with leucovorin 200 mg/m^2 i.v. over 2 hours, then 5FU 2,400 mg/m^2 over 46 hours (94–96). Palliative radiotherapy to the primary tumor of 30 Gy over two to three weeks was allowed if patients experienced worsening dysphagia and/or bleeding consistent with localized disease progression while all other systemic disease was controlled; systemic therapy was held during this time and then resumed one to two weeks after completion of radiotherapy.

All adverse events were graded according to the NCI Common Toxicity Criteria for Adverse Events version 4.0. Intrapatient dose reductions of oxaliplatin, irinotecan, docetaxel, and 5FU were allowed depending on the type and severity of toxicity; omitting the 5FU bolus was the first modification per protocol for most toxicities, upon which resuming the bolus in any subsequent cycle or line was not permitted. Additionally, any dose modifications to the 5FU or leucovorin were carried over to next-line therapies.

Patients began first-line FOLFOX therapy immediately while biomarker testing was initiated. Upon obtaining biomarker group assignment according to the algorithm (Table 2), the appropriate monoclonal antibody was added to the next scheduled dose of cytotoxic therapy, continuing every two weeks. Upon each disease progression (PD1 and PD2), patients changed to the next-line cytotoxic doublet while remaining on the prior assigned monoclonal antibody until PD1/PD2 molecular profiling results were obtained, upon which the appropriate antibody would be incorporated at the next scheduled dose of cytotoxic therapy.

Group 1 (IO) tumors received anti–PD-1 antibody, nivolumab 200 mg i.v. over 30 minutes. Group 2 (*HER2*-amplified) tumors received anti-HER2 antibody, trastuzumab 6 mg/kg loading dose on the first cycle then 4 mg/kg i.v., over 90 minutes and then 30 minutes if the initial infusion was well tolerated. Group 3 (*EGFR*-amplified) tumors received anti-EGFR antibody, ABT806 24 mg/kg i.v. over 30 minutes (97). When available, group 4 (*FGFR2*-amplified) tumors received anti-FGFR2 antibody, bemarituzumab (FPA-144) 15 mg/kg over 30 minutes (31, 35). Group 5 (*MET*-amplified) tumors did not have a monoclonal antibody available. Group 4 and group 5 tumors without available antibodies were treated with standard doublet cytotoxic therapy alone and considered non-ITT. Whenever possible, group 5 patients received off-label crizotinib 250 mg orally twice daily and/or cabozantinib 60 mg orally daily after failure of first-line cytotoxic therapy, and these patients were included in a preplanned mITT analysis. Group 6 (MAPK/PIK3CA) tumors received anti-VEGFR2 antibody, ramucirumab 8 mg/kg over 1 hour. Group 7 (EGFR expressing, nonamplified) tumors received anti-EGFR antibody, ABT806 24 mg/kg i.v. over 30 minutes. Group 8 (negative for all biomarkers or QNS) tumors received anti-VEGFR2 antibody, ramucirumab 8 mg/kg over 1 hour (50, 98). Dose modifications of monoclonal antibodies were not allowed, but could be delayed until resolution or stabilization of adverse events attributed to the antibody while continuing cytotoxic therapy alone.

To limit cumulative toxicity, oxaliplatin, irinotecan, and docetaxel were permitted to be stopped and resumed intermittently ("OPTIMOX," ref. 99; "OPTIMIRI," ref. 100; and "OPTITAX"), while continuing maintenance 5FU plus monoclonal antibody. Each line of therapy was considered to have failed only upon disease progression on the full cytotoxic doublet or progression on maintenance therapy but inability to resume the cytotoxic doublet for any reason. Patients were assessed for disease progression by imaging of the chest, abdomen, and pelvis every two months (four cycles). Patients had study treatment discontinued if they developed progressive disease as defined by RECIST1.1 after three lines of therapy, or earlier if unable to continue to the next treatment line for any reason. Other criteria for removal included withdrawal of consent or treatment-related adverse events not resolving after nine weeks of treatment interruption.

Outcomes

The primary efficacy endpoint of the study was one-year OS, defined as the proportion of patients treated with ITT alive at 12 months. All patients were followed for survival to the final data lock on August 20, 2020. Other primary endpoints were safety and feasibility; the molecular approach would be deemed safe if less than a 5% serious adverse event rate was observed from baseline and serial biopsies. The molecular approach would be deemed feasible if at least 85% of patients were assigned to therapy within two months of enrollment and if at least 85% of patients obtained a successful biopsy at PD1. Secondary endpoints included overall safety and tolerability; progression-free survival for each line of therapy ($PFS_{1,2,3}$) calculated as the time from starting each cytotoxic doublet until documentation of clinical or radiologic disease progression or death, whichever occurred first; objective response rate ($ORR_{1,2,3}$) by RECIST1.1 and disease control rate ($DCR_{1,2,3}$) for each line of therapy; and time to PANGEA treatment failure (TTF) among the patients treated with ITT. Outcomes were compared with historical outcomes and also those non-ITT patients having lack of availability of monoclonal antibodies (group 4 FGFR2 and group 5 MET). A preplanned mITT analysis included patients within group 5 able to get off-label tyrosine kinase inhibitors during their treatment course. Prespecified secondary analyses included analysis of OS, PFS, ORR, and DCR by individual biomarker group by treatment line, as well as contrasting the pooled outcomes of higher-priority groups 1–4 (or groups 1–5 for mITT) compared with lower-priority groups 6–8 of the algorithm, and also evaluating outcomes after excluding the effect of group 2 (HER2). Characterization of biomarker heterogeneity at baseline spatially and over time after targeted therapy were also secondary endpoints. Given the association with prognosis, an *ad hoc* characterization of baseline absolute NLR was performed, as previously described (75).

Statistical Analyses

Using a z-test based on the Greenwood standard error to accommodate censoring, 68 patients treated per ITT provided 80% power to detect an improvement in one-year OS rate from 50% historically to 63% with a one-sided alpha of 10%. Assuming exponential survival, this corresponds to an HR of 0.67. The historical 50% one-year rate implies a median of 12 months and was obtained as a weighted average of a sample comprised of 20% of patients having HER2-positive disease with an anticipated $H_{0\text{-}HER2+}$ mOS of 16 months and 80% of patients having HER2-negative disease with an anticipated $H_{0\text{-}HER2-}$ mOS of 11 months. [Of note, 16 of 80 (20%) of all patients enrolled, or 68 (23.5%) of the ITT, or 16 of 70 (22.9%) of the mITT patients in our study were HER2-positive.] Patients receiving at least one dose of first-line FOLFOX therapy and having availability of monoclonal antibody (though not necessarily receiving it) were considered

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evaluable for the primary outcome by ITT. Analysis of OS, PFS (during first, second, and third-line treatments), and TTF was estimated using Kaplan–Meier methods. All secondary endpoints including safety were assessed in all ITT patients who received at least one dose of first-line cytotoxic therapy. The log-rank test was used to compare OS, PFS, and TTF between various subgroups. All statistical analyses were done using Stata version 16.0 (StataCorp). This trial is registered with ClinicalTrials.gov (NCT02213289).

Authors' Disclosures

D.V.T. Catenacci reports personal fees from Lilly, Five Prime, BMS, Seattle Genetics, Merck, Taiho, Astellas, Pieris, Daiichi Sankyo, Zymeworks, QED, Gritstone, Foundation Medicine, Tempus, Guardant Health, Natera, and Archer, grants and personal fees from Genentech/Roche and Amgen, and non-financial support from Macrogenics and AbbVie during the conduct of the study. K. Roggin reports Intuitive Surgical subsidizes a portion of the author's robotic surgery training in 2017. M. Rampurwala reports other from AbbVie and AstraZeneca outside the submitted work. Y. Ji reports grants from NIH during the conduct of the study; personal fees from Astellas Pharma outside the submitted work; and Dr. Ji is a co-founder of Laiya Consulting, Inc., which has been acquired by Cytel, Inc. in August 2020. Laiya provides statistical consultation and develops software for pharmaceutical industry and drug developers. Dr. Ji is also a co-founder of Bayesoft, Inc., a startup company that works with Cytel only on consultation. T. Karrison reports grants from National Cancer Institute during the conduct of the study. C.-Y. Liao reports personal fees from Ipsen, Incyte, Lexicon, Exelixis, and Eisai outside the submitted work. B.N. Polite reports non-financial support from Tapestry Consulting and ICER outside the submitted work. H.L. Kindler reports personal fees and non-financial support from Inventiva, AstraZeneca, Merck, and Paredox and personal fees from Aldeyra, Bayer, Boehringer Ingelheim, BMS, Erytech, Five Prime, Deciphera, and Kyowa outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

D.V.T. Catenacci: Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **S. Moya:** Data curation, investigation, project administration, writing–review and editing. **S. Lomnicki:** Data curation, investigation, project administration, writing–review and editing. **L.M. Chase:** Data curation, investigation, project administration, writing–review and editing. **B.F. Peterson:** Data curation, investigation, project administration, writing–review and editing. **N. Reizine:** Investigation, writing–review and editing. **L. Alpert:** Data curation, writing–review and editing. **N. Setia:** Data curation, writing–review and editing. **S.-Y. Xiao:** Data curation. **J. Hart:** Data curation. **U.D. Siddiqui:** Data curation, writing–review and editing. **D.K. Hogarth:** Data curation, writing–review and editing. **O.S. Eng:** Data curation, writing–review and editing. **K. Turaga:** Data curation, writing–review and editing. **K. Roggin:** Data curation, writing–review and editing. **M.C. Posner:** Data curation, writing–review and editing. **P. Chang:** Data curation, writing–review and editing. **S. Narula:** Data curation, investigation, writing–review and editing. **M. Rampurwala:** Data curation, investigation, writing–review and editing. **Y. Ji:** Data curation, methodology, writing–review and editing. **T. Karrison:** Conceptualization, formal analysis, validation, methodology, writing–review and editing. **C.-Y. Liao:** Data curation, investigation, writing–review and editing. **B.N. Polite:** Conceptualization, supervision, investigation, visualization, methodology, writing–review and editing. **H.L. Kindler:** Conceptualization, supervision, investigation, methodology, writing–review and editing.

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